Clinical and Neuropathologic Findings in a Woman With the\nFMR1 Premutation and Multiple Sclerosis

Claudia M. Greco, MD; Flora Tassone, PhD; Dolores Garcia-Arocena, PhD; Nicole Tartaglia, MD; Sarah M. Coffey, MPH; Timothy K. Vartanian, MD, PhD; James A. Brunberg, MD; Paul J. Hagerman, MD, PhD; Randi J. Hagerman, MD

Background: Multiple sclerosis (MS) and fragile X–associated tremor/ataxia syndrome (FXTAS) have overlapping clinical signs and symptoms.

Objectives: To present a case with evidence of both MS and FXTAS and to discuss the relationship of both disorders.

Design: Case report.

Setting: Fragile X Research and Treatment Center at the University of California, Davis, Medical Center.

Patient: Woman with the FMR1 premutation who died of MS at the age of 52 years.

Main Outcome Measures: Magnetic resonance imaging, physical examination, and neuropathologic examination results.

Results: Magnetic resonance imaging, physical examination, and autopsy neuropathologic examination revealed diagnostic features of MS and FXTAS.

Conclusion: The molecular mechanism of RNA toxicity, including the elevation of \( \alpha \)B-crystallin levels observed in FXTAS, may lead to enhanced predisposition to autoimmune diseases.

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MULTIPLE SCLEROSIS (MS), the most common demyelinating disease of the central nervous system (CNS), affects more than 350,000 people in the United States and an estimated 2 million people worldwide; CNS demyelination and varying degrees of axonal injury and inflammation are essential features in established cases. The consistent presence of axonal dysfunction has furthered an understanding of sustained disability and regenerative failure in those with MS.1

Premutation alleles (55–200 CGG repeats) of the fragile X mental retardation 1 (FMR1) gene are common (1 per 100–300 females and 1 per 300–800 males); toxic effects caused by the excess amount of premutation FMR1 messenger RNA (mRNA) leads to the adult-onset neurologic disorder fragile X–associated tremor/ataxia syndrome (FXTAS).2 The penetrance of FXTAS in male carriers throughout 50 years, ascertained through families with a fragile X syndrome proband, is approximately 40%; its penetrance in female carriers is lower (approximately 5%–10%).2,3 The pathologic features of FXTAS include intranuclear inclusions in neurons and astrocytes throughout the brain and brainstem, astrocyte activation, axonal retraction bulbs, axonal loss, and myelin loss.4,5 The inclusions contain \( \alpha \)B-crystallin, MBP, lamin A/C isoforms, and numerous other proteins.5 The toxic effects of FMR1 mRNA also result in the disruption of nuclear lamin A/C architecture and formation of perinuclear \( \alpha \)B-crystallin aggregates in cultured neural cells.6

A 32-year-old woman presented with right arm numbness that persisted for 2 months, followed by an episode of optic neuritis; both resolved spontaneously. At 38 years of age, she presented with a left extensor plantar reflex, loss of dexterity in the right hand, appendicular ataxia that involved the right lower extremity, and mild gait ataxia. Brain magnetic resonance imaging (MRI) revealed mild diffuse atrophy and multiple foci of increased T2-weighted signal intensity in the periventricular white matter and cerebellum, consistent with a demyelinating disorder (Figure 1). She was diagnosed as having relapsing-remitting MS. Lumbar puncture was not performed. Despite treatment, her condition deteriorated during the next 3 months, with reducing bilateral lower extremity sensation and motor function, worsening ataxia, and frequent urinary incontinence. At 43 years of age, progression involved bilateral hand and lower extremity numbness, upper extremity intention tremor, gait ataxia, spastic paraparesis, short-term memory deficits, progressive dysthria, disinhibition, and depression. During the next 9 years, additional medications, including
weekly methotrexate, interferon beta-1b, and mitoxantrone, were used. Her family history includes parkinsonism in her maternal grandfather and ovarian dysfunction (mid-30s) in her daughter, with workup revealing a premutation FMR1 allele (84 repeats). No other family history of fragile X syndrome was found. Given her daughter’s carrier status and her own neurologic problems, the patient was tested and found to have a premutation allele (75 repeats). The activation ratio (fraction of normal active FMR1 alleles) was 0.44. The FMR1 RNA level was elevated (mean [SD], 2.80 [0.12] times normal), consistent with premutation carrier status. She died at the age of 52 years after progressive memory impairment, loss of motor control, significant ataxia, and tremor.

Coronal sections of the brain (1133 g) showed moderate frontal gyral atrophy, with scattered, variably sized, discrete regions of gray discoloration in cerebral and cerebellar white matter, especially prominent in periventricular locations but also in the basal ganglia, brainstem, and left middle cerebellar peduncle. On microscopic examination, these abnormalities appeared as areas of demyelination in various stages of activity (Figure 2). Microfoci of perivascular parenchymal pallor with lymphocytic infiltrates were present in early lesions. Midstage plaques showed infiltrates of foamy macrophages and lymphocytes, reactive astrocytosis, and microglial activity at their margins; scant perivascular mononuclear inflammatory infiltrates were also seen (Figure 2A). Inactive plaques showed parenchymal collapse with microcystic change. Correspondingly, Bielschowsky (axon) stain and Luxol fast blue/periodic acid–Schiff (myelin) stain showed varying degrees of axonal and myelin loss, respectively. Patchy areas of demyelination were seen in the molecular layers of both the cerebrum and cerebellum. Immunocytochemical staining for CD4+ lymphocytes (helper T cells) was negative in subacute lesions and revealed scant positive cells in a burned-out plaque (Figure 2C); CD8+ lymphocytes (killer T cells) were common in subacute plaques and scant in chronic plaques (Figure 2D). CD20 (B-cell) immunostaining was negative in both. Glial fibrillary acidic protein immunostaining showed reactive astrocytes in and around plaques and in nearby gray matter.

Ubiquitin immunostaining identified few intranuclear inclusions in astrocytes throughout the brain and rare inclusions in cortical neurons, as described for FXTAS. Astrocytic inclusions were within regions of de-
myelinated white matter (Figure 2B) and nondemyelinated white matter.

**COMMENT**

This report describes a woman with MS, clinically definite on the basis of accepted criteria but with evidence of both MS and FXTAS on neuropathologic study results. Symptoms and findings shared by these disorders include intention and head tremor, ataxia, peripheral neuropathy, and spasticity. This patient’s MRI abnormalities are compatible in distribution and in time-related alterations with the diagnosis of MS. The cerebral white matter T2-weighted signal intensity alterations that occur with FXTAS generally involve subependymal, deep, and subcortical white matter and are usually more confluent than is seen with typical MS; however, in an individual patient, these features cannot be definitely distinguished from changes that may be associated with extensive MS. The diffuse white matter MRI signal intensity alterations in this patient, although more characteristic of MS, may represent independent, additive imaging abnormalities for the 2 disorders.

It is possible that FXTAS and MS may be coincident, that the underlying disease process in FXTAS may manifest clinically as MS on some occasions, or that FXTAS may stimulate the pathologic process of MS, exacerbating its course. Indeed, Hall et al found that 2 of 56 patients with FXTAS were initially diagnosed as having MS or possible MS. In a separate cohort of 125 female premutation carriers without FXTAS, 1 patient was also diagnosed as having MS based on MRI findings, neurologic examination findings, and the presence of oligoclonal bands in the cerebrospinal fluid.

Several mechanisms may contribute to a potential causal relationship between MS and FXTAS. The small heat shock protein aB-crystallin is thought to be involved both in the normal dynamics of cytoskeletal proteins and in maintenance of cell survival during cellular stress. aB-crystallin is highly expressed during the early phases of MS episodes, and autoantibodies to aB-crystallin are found in the cerebrospinal fluid of patients with MS, potentially interfering with its protective role in reducing brain inflammation and brain cell death. aB-crystallin is also found within CGG repeat–induced inclusions of patients with FXTAS, possibly reflecting an early response to cellular stress imposed by the toxic FMR1 mRNA and disruption of lamin A/C architecture within the nucleoplasm.

Recent observations (C.M.G., F.T., D.G.-A., et al, unpublished data, June 14, 2007) found that the aB-crystallin mRNA levels were significantly higher in the frontal cortex of patients with FXTAS compared with control patients. Because aB-crystallin is a key antigen in the development of MS, upregulation of aB-crystallin in patients with FXTAS could result in loss of immunologic tolerance, leading to predisposition or exacerbation of MS. Furthermore, carrier women appear to be particularly prone to develop autoimmune disorders, including autoimmune thyroiditis and fibromyalgia. We therefore hypothesize that the elevation of aB-crystallin levels observed in FXTAS may lead to enhanced predisposition to autoimmune diseases.

In conclusion, additional studies regarding the association of MS and FXTAS are warranted. The screening of individuals with atypical MS for the FMR1 premutation is also recommended, particularly if there is a family history of primary ovarian insufficiency, developmental delay, autism, intention tremor, ataxia, or neuropathy.

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**Correspondence:** Randi J. Hagerman, MD, M.I.N.D. Institute, University of California, Davis, Health System, 2825 50th St, Sacramento, CA 95817 (randi.hagerman@ucdmc.ucdavis.edu).

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